REMARKS

Upon entry of this paper, claims 34, 91-94, 96-100, 106, 109-110 and 115-116 will be pending and under consideration. Claims 101-105, 108, 111, 113, 114 and 116 have been withdrawn from consideration due to a species election. Claims 34 and 105 have been amended for reasons of clarity. Claim 34 has been amended to specify that the molecule is (i) a protein capable of inhibiting the interaction of said human Notch protein with another toporythmic protein, or (ii) an antibody to said human Notch protein or a portion of said antibody containing the idiotype thereof, or (iii) an oligonucleotide which (a) consists of at least six nucleotides, (b) consists of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene; and (c) is hybridizable to the RNA transcript. Support for this amendment is found in the specification at page 11, line 16; page 11, lines 20-22; page 12, lines 3-4; page 14, line 1; page 30, line 29 to page 31, line 5; page 31, lines 28-30; and page 57, lines 7-8. In view of the amendment to claim 34, claim 105 has been amended to recite solely that the oligonucleotide consists of at least a sequence complementary to at least a portion of a RNA transcript of a Notch gene.

No new matter has been added by the amendments to the claims.

1. The Rejection under 35 U.S.C. § 112, First Paragraph, Is In Error

Claims 34, 91-94 and 115 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, even though the Examiner indicates that antibodies to human Notch, fragments of such antibodies containing the idiotype, and Notch antisense nucleic acids meet the written description requirement, the Examiner alleges that the use of a broad genus of antagonistic molecules is not adequately supported in the present disclosure. Applicants respectfully disagree with the Examiner's rejection and submit that the present specification provides a sufficient written discretion of the claimed invention, as amended herein.

Preliminarily, Applicants point out that claim 34 has been amended to recite that the antagonist molecule is (i) a protein capable of inhibiting the interaction of said human Notch protein with another toporythmic protein, or (ii) an antibody to said human Notch protein or a

portion of said antibody containing the idiotype thereof, or (iii) an oligonucleotide which (a) consists of at least six nucleotides, (b) consists of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene; and (c) is hybridizable to the RNA transcript. Applicants note that toporythmic genes are defined in the specification on page 5, lines 25-31:

> Toporythmic genes, as used herein, shall mean the genes Notch, Delta and Serrate, as well as other members of the Delta/Serrate family which may be identified by virtue of sequence homology or genetic interaction, and in general, members of the "Notch cascade" or the "Notch group" of genes, which are identified by molecular interactions (*e.g.*, binding *in vitro*) or genetic interactions (as detected phenotypically, *e.g.*, in *Drosophila*).

Thus, in view of this amendment, the antagonist molecule of the claims is one that directly inhibits the Notch pathway either as a protein capable of inhibiting the interaction of a human Notch protein with another toporythmic protein (for example, an antibody to a Notch, Delta or Serrate protein or a competitive inhibitor of such binding), or as an oligonucleotide complementary to at least a portion of a toporythmic gene (for example, a Notch, Delta or Serrate gene).

In order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, an Applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). This inquiry is often phrased as whether the patent specification provides "adequate support" for the claim(s) at issue. *Id.* at 1560. Moreover, a claimed genus may be satisfied through sufficient description of relevant identifying characteristics of a representative number of species. *See, Regents of University of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied* 523 U.S. 1089 (1998). What constitutes a "representative number of species" depends upon the knowledge and skill in the art. Moreover, such a description need not be sufficient to provide support to claim each individual species encompassed by the genus. The description is deemed sufficient if it demonstrates to the skilled artisan that the applicant was in possession of the necessary common attributes of the members of the genus. *Eli Lilly*, 119 F.3d at 1568.

As noted above, the Examiner acknowledges that antibodies that specifically bind to human Notch protein, antibodies containing the idiotype thereof, and Notch antisense nucleic acids meet the written description requirement. Regarding the "protein capable of inhibiting the interaction of a human Notch protein with another toporythmic protein, "Applicants submit that such a protein is fully described by the specification within the meaning of 35 U.S.C. § 112, first

paragraph. As explained above, toporythmic proteins are those proteins that are members of the Notch group of genes that interact molecularly or genetically. Further, Applicant points out that human Notch and a representative number of other toporythmic proteins, *i.e.*, members of the Notch group of genes, were known and characterized at the time the invention was made, including Delta, Serrate, Mastermind, Suppressor of Hairless and Hairless (see, the specification, *e.g.*, at page 1, line 22 to page 3, line 4; page 5, lines 25-31). For example, in the present specification two human Notch amino acid and nucleotide sequences are set forth (see Figures 10, 11, 13 and 17). Further, the nucleotide and amino acid sequences of *Drosophila* Notch are depicted in Wharton *et al.*, 1985, Cell 43:567-581 (Ref. C72, of record). The amino acid sequence of *Xenopus* Notch is depicted in Coffman *et al.*, 1990, Science 249:1438-1441 (Ref. C14, of record). Further, *Drosophila* Delta and *Drosophila* Serrate nucleotide and amino acid sequences are disclosed in Kopczynski *et al.*, 1988, Genes Dev 2:1723-1735 (Ref. C39, of record) and Fleming *et al.*, 1990, Genes Dev 4:2188-2201 (Ref. C23, of record), respectively. *Drosophila* Suppressor of Hairless, *Drosophila* Mastermind and *Drosophila* Hairless nucleotide and amino acid sequences are disclosed in Schweisguth *et al.*, 1992, Cell 69(7):1199-1212 (Ref. C118, made of record in the Supplemental Information Disclosure Statement submitted herewith), Smoller *et al.*, 1990, Genes Dev 4:1688-1700 (Ref. C119, made of record in the Fourth Supplemental Information Disclosure Statement submitted herewith), and Maier *et al.*, 1992, Mech. Dev. 38(2):143-156 (Ref. C120, made of record in the Fourth Supplemental Information Disclosure Statement submitted herewith), respectively.

Further, the specification teaches and/or one skilled in the art would recognize in view of the teachings of the specification and the art, a number of protein antagonists which are capable of inhibiting the interaction of a human Notch protein with another toporythmic protein. For example, and not by way of limitation, such proteins are anti-toporythmic protein antibodies, and competitive inhibitors of Notch protein-protein interactions (such as a protein comprising Notch ELR-11 and ELR-12 (the adhesive or binding region of Notch responsible for binding to Delta and Serrate), a protein comprising the binding domain of a Serrate protein or the binding domain of a Delta protein) and dominant negative mutants of toporythmic proteins. See the specification, *e.g.*, at page 12, lines 2-5, page 16, lines 22-24, and at page 57, lines 23-26.

In view of the fact that toporythmic proteins are well known in the art, and in view of the known functional and structural characteristics of antibodies and fragments thereof, an antibody to a toporythmic protein meets the written description requirements of Section 112 since the toporythmic proteins are uniquely identified and distinguished from other proteins. Further, the specification teaches the amino acid sequences within the toporythmic proteins Notch, Delta and

Serrate that are required for protein-protein interaction with other toporythmic proteins (see Sections 7-8 on pages 67-77). Thus, the specification enables competitive inhibitor proteins consisting of or comprising these binding domains.

In view of the foregoing, Applicants respectfully submit that sufficient representative species of "proteins that are capable of inhibiting the interaction of a human Notch protein with another toporythmic protein" and their relevant identifying characteristics have been taught by the specification. Thus, the genus of "proteins that are capable of inhibiting the interaction of a human Notch protein with another toporythmic protein" is adequately described and the written description requirement of Section 112 has been met.

Further, Applicants submit that an oligonucleotide which (a) consists of at least six nucleotides, (b) consists of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene; and (c) is hybridizable to the RNA transcript also meets the written description requirement of Section 112, first paragraph, for reasons similar to those detailed above. As set forth above, sequences of many toporythmic genes were either described in the specification or were known in the art at the time the invention was made. In view of this knowledge, one skilled in the art would recognize that Applicants were in possession of oligonucleotides having sequences complementary to at least a portion of a RNA transcript of such toporythmic genes. Since the genus of toporythmic genes is sufficiently described under Section 112, first paragraph, a genus of oligonucleotides having sequences complementary to at least a portion of a RNA transcript of a toporythmic gene also is sufficiently described to meet the written description requirement under Section 112, first paragraph.

Thus, a molecule which antagonizes the function of a human Notch protein, wherein said molecule is (i) a protein capable of inhibiting the interaction of said human Notch protein with another toporythmic protein, or (ii) an antibody to said human Notch protein or a portion of said antibody containing the idiotype thereof, or (iii) an oligonucleotide which (a) consists of at least six nucleotides, (b) consists of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene; and (c) is hybridizable to the RNA transcript, meets the written description of Section 112, first paragraph.

In view of the foregoing, Applicants respectfully request withdrawal of this Section 112, first paragraph, rejection.

2. The Rejection under 35 U.S.C. § 112, First Paragraph, Is In Error

Claims 34, 91-94 and 115 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, allegedly, does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. According to the Examiner, the specification does not reasonably provide enablement for a method of treating malignancies by administering any molecule which antagonizes the function of a human Notch protein. Applicants respectfully disagree with the Examiner and submit that the full scope of the presently pending claims, as amended herein, can be practiced by one skilled in the art without undue experimentation, and thus, the presently pending claims meet all the requirements set forth under 35 U.S.C. § 112, first paragraph.

As discussed above, claim 34 has been amended to recite that the antagonist molecule is (i) a protein capable of inhibiting the interaction of said human Notch protein with another toporythmic protein, or (ii) an antibody to said human Notch protein or a portion of said antibody containing the idiotype thereof, or (iii) an oligonucleotide which (a) consists of at least six nucleotides, (b) consists of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene; and (c) is hybridizable to the RNA transcript. Also, as discussed above, such an antagonist molecule so specified meets the written description requirement of Section 112, first paragraph.

Applicants respectfully disagree with the Examiner's enablement rejection with regard to any molecule that antagonizes the function of a human Notch protein, and submit that the specification clearly enables one of skill in the art to practice the full scope of the claimed methods, as amended herein, without undue experimentation. Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, *i.e.*, the key word is " undue", not "experimentation". *Id.*

Applicants submit that the specification provides considerable guidance and direction to practice the claimed invention without undue experimentation and incorporate by reference their

remarks made in the Reply dated February 11, 2008 and in the Reply dated November 14, 2008 submitting that one skilled in the art would not have to engage in undue experimentation in order to practice the claimed invention, and present additional remarks below. Further, Applicants point out that the specification and post-filing date evidence[1] show that a molecule which is (i) a protein capable of inhibiting the interaction of said human Notch protein with another toporythmic protein, or (ii) an antibody to said human Notch protein or a portion of said antibody containing the idiotype thereof, or (iii) an oligonucleotide which (a) consists of at least six nucleotides, (b) consists of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene; and (c) is hybridizable to the RNA transcript, can disrupt Notch function. In fact, the Examiner has presented no evidence to the contrary.

The Examiner's attention is respectfully directed to the following post-filing date references, which demonstrate the ability of proteins that are capable of inhibiting the interaction of a Notch protein with another toporythmic protein, including but not limited to antibodies to the toporythmic proteins Notch, Delta and Jagged (mammalian Serrate), and oligonucleotides which consist of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene to inhibit Notch function and the usefulness of such molecules in the treatment of malignancy.

Moellering *et al*, 2009, Nature 462(12):182-188 ("Moellering") (Ref. C121, made of record in the Fourth Supplemental Information Disclosure Statement submitted concurrently herewith) discloses a peptide inhibitor (SAHM1) of the interaction between a complex of the Notch intracellular domain (ICN1) and the toporythmic protein Suppressor of Hairless (CSL) with another toporythmic protein Mastermind (MAML). See, Abstract; page 182 left column, second paragraph, and page 184, left column, first paragraph. SAHM1 inhibited the proliferation of T-ALL cells in culture (page 185, left and right columns). Moreover, SAHM1, when administered to mice with established T-ALL, resulted in a significant dose-dependent regression of tumor, and this anti-leukemic effect was shown to be associated with decreased Notch1 target gene expression (page 186, left and right columns). These results indicate that a protein capable of inhibiting the interaction of a Notch protein with another toporythmic protein can antagonize Notch function, and be useful in the treatment of a malignancy.

Veeraraghavalu *et al.*, 2004, J. Virology 78:8687-8700 ("Veeraraghavalu") (Ref. C93 of record) discloses that inhibiting Notch signaling inhibited the tumorigenicity of a transformed cell line in nude mice, which cell line was previously shown to be susceptible to growth

[1] Applicants note that post filing date references can be used to show the accuracy of a statement made in the specification. See *Application of Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A., 1971), fn. 4.

inhibition by inhibiting Notch expression (Abstract). Veerarghavalu on page 8698, left column, explains that by inhibiting Notch signaling function by expressing soluble Jagged1 (Jagged is mammalian Serrate), Manic Fringe and siRNA against Jagged1 the tumorigenicity of CaSki cells *in vivo* could be blocked, which is consistent with a role for Notch signaling in maintaining the neoplastic phenotype. These results indicate that a competitive inhibitor of Notch-ligand binding (*e.g.*, soluble Jagged1), as well as an oligonucleotide consisting of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene (*e.g.*, Jagged siRNA) can antagonize Notch function, and be useful in the treatment of a malignancy.

Purow *et al.*, 2005, Cancer Res. 65(6):2353-2363 ("Purow") (Ref. C88 of record) shows that down-regulation of Notch, Delta or Jagged (Serrate) induces apoptosis and inhibits proliferation of multiple glioma cell lines (see Abstract). Purow shows that pre-treatment of glioma cells with the antagonists of Notch function, Notch-1 siRNA or Delta-like-1 siRNA, significantly prolonged survival of mice implanted intracranially with the glioma cells as compared to mice implanted with control glioma cells (see page 2360, right column to page 2361, left column and Figures 4F and 5C). These results indicate that an oligonucleotide consisting of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene can antagonize Notch function and be useful in the treatment of malignancy. These results indicate that an oligonucleotide consisting of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene (*e.g.*, Notch-1 siRNA and Delta-like-1 siRNA) can antagonize Notch function, and be useful in the treatment of a malignancy.

Kiaris *et al.*, 2004, Am. J. Pathology 165:695-705 ("Kiaris") (Ref. C81 of record) demonstrates that the Notch antagonist Deltex can inhibit human-ras1-driven, cyclin D1-dependent mammary oncogenesis in cells expressing endogenous levels of Notch. These results suggest that antagonizing Notch can be therapeutically useful in the treatment of malignancies.

Wu *et al.*, Stabilizing Receptor Quiescence with Synthetic Antibodies Enables Precise Control of Notch Signaling In Vivo, Submitted Manuscript, (Ref. C124, made of record in the Fourth Supplemental Information Disclosure Statement submitted herewith) ("Wu") discloses the production of two monoclonal antibodies, one specific for Notch1, and the other specific for Notch2, which antibodies specifically inhibit Notch1 and Notch2 function *in vitro* and *in vivo*, respectively (see pages 8-13). Further, on pages 17-18, Wu discloses that the antibody specific to Notch1 was able to inhibit tumor growth in preclinical models. Applicants submit that such data clearly shows that anti-Notch antibodies are capable of acting as antagonists of Notch function and indicates that such antibodies can be useful in the treatment of a malignancy.

Li *et al.*, J. Biol. Chem., E-published Jan 8., 2008, (Ref. C103 of record) discloses the development of monoclonal antibodies (A4 and A8) against Notch3, which are able to inhibit the activation of Notch3 by multiple DSL ligands. Further, these antibodies also inhibited Jagged 1-induced up-regulation of *HES5* and *HEY2*, two well-characterized Notch pathway genes (paragraph bridging pages 4-5). Applicants submit that such data clearly shows that anti-Notch antibodies are capable of acting as antagonists of Notch function.

Krop *et al.*, 2006, Abstract 6097, Breast Cancer Research and Treatment 100:Supplement 1 ("Krop") (Ref. C107 of record) presents data from a phase I pharmacokinetic and pharmacodynamic trial of the novel oral Notch inhibitor MK-0752 (a γ-secretase inhibitor) in patients with advanced breast cancer and other solid tumors. Krop reports that a significant decrease in Notch intracellular domain expression was observed in post-treatment tissue biopsies, indicating that Notch function was being inhibited.

Kogoshi *et al.*, 2007, Oncology Reports 18:77-80 ("Kogoshi") (Ref. C104 of record) teaches that γ-secretase inhibitors block Notch activation and can suppress the growth of acute T-lymphoblastic leukemia (T-ALL) cells with Notch 1 mutations, as well as some types of B-ML and AML cells, and that clinical trials of a γ-secretase inhibitor have begun in the United States for refractory T-ALL (see Abstract, page 77, right column and page 80, right column).

Park *et al.*, 2006, Cancer Res. 66:6312-6318 ("Park") (Ref. C105 of record) discloses that a human Notch gene, Notch3, was the gene that showed the most significant amplification in amplified ovarian serious carcinomas, and that inactivation of Notch3 by both γ-secretase inhibitor and Notch3-specific small interfering RNA suppressed cell proliferation and induced apoptosis in cell lines that overexpressed Notch3 but not in those with minimal amount of Notch3 expression. Park states that the results indicate that Notch3 is required for proliferation and survival of Notch3-amplified tumors and that inactivation of Notch3 can be a potential therapeutic approach for ovarian carcinomas (Abstract). Park concludes on page 6317, right column that "[o]ur findings suggest that Notch3 amplification may play an important role in the development of ovarian carcinomas; moreover, these findings provide a rationale for future development of Notch3-based therapy for ovarian cancer."

Konishi *et al.*, 2007, Cancer Res. 67:8051-8057 ("Konishi") (Ref. C106 of record) discloses that the γ-secretase inhibitor (MRK-003) inhibited Notch signaling, inhibited serum independence, and, *in vitro* and *in vivo*, reduced tumor cell growth and induced apoptosis in lung cancer cells (Abstract). Konishi states in the Abstract that "inhibition of Notch receptor activation represents a compelling treatment strategy."

Farnie *et al.*, 2007, Stem Cell Rev. 3:169-175 ("Farnie I") (Ref. C108 of record) discloses that inhibition of Notch using a γ-secretase inhibitor or a Notch 4 neutralizing antibody reduced DCIS mammosphere forming efficiency (MFE) (page 173, right column), indicating that "Notch signaling and other stem cell self-renewal pathways may represent novel therapeutic targets to prevent recurrence of pre-invasive and invasive breast cancer" (page 169, right column). On page 173, right column, Farnie I states that their results suggest that targeting both of these pathways (anti-Notch antibody and γ-secretase inhibitor) may have therapeutic value for DCIS.

Farnie *et al.*, 2007, J. Natl. Cancer Inst. 99:616-627 ("Farnie II") (Ref. C109 of record) discloses that ductal carcinoma in situ (DCIS) is a noninvasive breast malignancy that, if untreated, progresses to invasive cancer in 30% to 50% of patients (page 616, left column), and that treatment of DCIS tissue samples with the γ-secretase inhibitor DAPT or with Notch 4 neutralizing antibody reduced DCIS mammosphere forming efficiency, suggesting that the Notch receptor signaling pathway is directly involved in the regulation of DCIS mammosphere formation and/or growth (page 624, right column). Farnie II states on page 626, left column that the data strongly suggest that targeting the Notch pathway would be therapeutically useful in treating DCIS.

Dontu *et al.*, 2004, Cancer Res. 6:R605-R615 ("Dontu") (Reference C110 of record) discloses that mammospheres, when grown in a three-dimensional culture system, develop extensive ductal lobuloalveolar structures similar in morphology to those found *in vivo* (see page R611, right column). When such mammosphere three-dimensional cultures were exposed to an inhibitor of Notch function, *i.e.*, a γ-secretase inhibitor or an anti-Notch antibody, the branching morphogenesis was completely inhibited (page R611, right column). Dontu explains that the results presented suggest that Notch signaling plays a critical role in normal human mammary development and that abnormal Notch signaling may contribute to mammary carcinogenesis by deregulating the self-renewal of normal mammary stem cells (Abstract).

The Examiner is also respectfully directed to the discussion of references Reedijk, Büchler, Nam, Jundt, Miele, Jang, Hoek, Hayashi, Dang, Patel, Santagata, and Harper (all of record) on pages 15-20 in the Reply with Amendment filed on February 11, 2008, which show that activated Notch function is associated with malignancy, and suggest that antagonizing Notch can be therapeutically useful in the treatment of malignancies.

The Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*,

the Federal Circuit explained the legal standard for compliance with the relevant Section 112 requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, the Federal Circuit in *Brana* explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1441. Regarding the claimed invention, Applicants have provided such evidence showing, *inter alia*, that (i) a protein capable of inhibiting the interaction of a Notch protein with another toporythmic protein, (ii) an antibody to a Notch protein, or (iii) an oligonucleotide complementary to at least a portion of a RNA transcript of a toporythmic gene, can antagonize Notch function, that activated Notch function is associated with malignancy, and that antagonizing the function of a Notch protein has anti-tumor therapeutic value in animal models (see Moellering, Purow, Konishi, Veeraraghavalu and Kiaris).

The foregoing evidence is sufficient to convince one skilled in the art of Applicants' asserted utility, *i.e.*, that antagonists of Notch function (*e.g.*, a protein capable of inhibiting the interaction of a human Notch protein with another toporythmic protein; an antibody to a human Notch protein or a portion of said antibody containing the idiotype thereof; or an oligonucleotide which (a) consists of at least six nucleotides, (b) consists of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene; and (c) is hybridizable to the RNA transcript) can be used to treat a malignancy. The claimed invention thus satisfies 35 U.S.C. § 112, first paragraph.

With regard to the Examiner's statement on page 12 of the present Office Action that undue experimentation would be required to determine which of the multitude of molecules in the Notch signaling pathway could be antagonized in order to obtain predictable therapeutic results, Applicants note that the evidence presented above demonstrates that the Notch signaling pathway has been inhibited (i) at the point of Notch-ligand binding by use of an antibody to block Notch-ligand binding, by use of an oligonucleotide (siRNA) to inhibit expression of Notch or Notch ligand, or by use of a competitive inhibitor of Notch-ligand binding; (ii) at the point of Notch receptor processing after ligand binding by use of a γ-secretase inhibitor; and (iii) at the point of formation of a Notch transcriptional complex (inhibiting ICN1-CSL binding to MAML) by use of the SAHM1 peptide, all with the same results, *i.e.*, inhibition of Notch function. Applicants submit that it would not be undue experimentation to determine which molecule of the Notch pathway could be antagonized since the data leads one skilled in the art to reasonably

predict that antagonizing any molecule of the Notch pathway will antagonize Notch function and provide predictable therapeutic results in the treatment of malignancies.

In view of the foregoing remarks, it is respectfully submitted that the specification provides sufficient teaching to allow one of skill in the art to successfully practice the claimed invention without undue experimentation. Thus, this rejection of claims 34, 91-94 and 115 under 35 U.S.C. § 112, first paragraph, should be withdrawn.

3. Withdrawn Claims

On December 14, 2006, the Examiner required a species election, and in response Applicants elected the species "Antibody to Notch." In view of this election, claims 101-106, 108-111, 113, 114 and 116 were withdrawn. As provided by 37 C.F.R. § 1.141, Applicants request consideration of withdrawn claims 101-106, 108-111, 113, 114 and 116, which are directly or indirectly dependent from claim 34. Applicants submit that claim 34 is an allowable generic claim and the withdrawn claims are written in dependent form or otherwise include all the limitations of claim 34, as required by 37 C.F.R. § 1.141.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks of the present response be entered and made of record in the file history of the present application.

Applicants request that the Examiner call Adriane M. Antler at (212) 326-3939 if any questions or issues remain.

Respectfully submitted,

Date: December 21, 2009

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Enclosures